REMARKS/ARGUMENTS

Claims 1-104 are pending in the present application. In this amendment, claims 11, 25, 26, 28, 31, 33-65, 75, 89, 90, 92 and 95 are amended and claims 97 and 98 are canceled without prejudice. Applicants' reserve the right to pursue all or portions of the subject matter in these amended and canceled claims in a subsequently filed divisional or continuation application. Claims 11, 25, 26, 28, 43, 57, 58, 60, 63, 75, 89, 90, 92, and 95 are amended to correct typographical errors. Applicants acknowledge and appreciate the Examiner's consideration of Applicants' IDS, specifically the abstracts of Japanese patents 10175964, 10175965, 11106340, 11116481, and Japanese patent publication 2000 229959. These abstracts are listed in the "Other Documents" of the concurrently filed Supplemental IDS.

Rejection of Claims 65-97 under 35 U.S.C. § 101

The Patent Office rejected claims 65-97 under 35 U.S.C. § 101 as not supported by a well established utility. Applicants respectfully assert that this rejection is improper request that it be withdrawn. Applicants acknowledge and appreciate the Patent Office's indication that claims 1-32 directed to compounds which are, for example, modulators of STAT6 are allowed and satisfy 35 U.S.C. §101. Applicants also acknowledge and appreciate the Patent Office's indication that method claims 65-97 have utility to the extent that they ameliorate adverse conditions. Applicants point out that the USPTO's *Utility Guidelines* state that:

> For method claims that recite more than one utility and one of those is credible, no rejection under 35 U.S.C. § 101 should be made. If any utility in such a claim is not credible, e.g., the claim recites both a credible utility and a utility that is not credible, the presence of the utility that is not credible should be addressed under 35 U.S.C. § 112, first paragraph, scope of enablement.
>
> (Revised Interim Utility Guidelines Training Materials p. 3).

In view of the Patent Office's examination guidelines and acknowledgement of the credible utility of the compounds and methods which ameliorate adverse conditions, Applicants request that this rejection be withdrawn. Any rejection of these claims as non-enabled is addressed below.

Rejection of Claims 33-104 under 35 U.S.C. § 112, First Paragraph

Additionally, the Examiner rejected claims 33-104 under 35 U.S.C. § 112, first paragraph as non-enabled. Applicants acknowledge and appreciate the Patent Office's indication that claims 1-32 directed to compounds which are, for example, modulators of STAT6 are allowed and satisfy 35 U.S.C. §112. Applicants also acknowledge and appreciate the Patent Office's acknowledgment that STAT6 is a component in airway hyperresponsiveness following allergen sensitization and challenge. However, the Patent Office appears to be requiring that Applicants show that their compositions and methods inhibit STAT6 and treat asthma *in vivo* as well as show how they work. Applicants respectfully assert that such a showing is not required to enable the claimed invention. *In re Brana* is usually cited for the proposition that *in vivo* studies are not a requisite for patentability and that demonstrated activity in an *in vitro* experimental model that is considered reasonably correlative of success *in vivo* is sufficient to satisfy the enablement requirement.[1] Even for an *in vitro* model to be enabling, a rigorous or an invariable exact correlation is not required.[2]

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[1] *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). *Brana* concerned the patentability of a composition. The *Brana* court stated that it needed to find only enabled utility to support the composition claim. A single enabled utility (i.e., efficacy against a single tumor type in an *in vitro* assay) was considered sufficient to support enablement of a claimed composition.

[2] *Cross v. Iizuka*, 753 F.2d 1040, 1050, (Fed. Cir. 1985) (holding a claim to a method of alleviating inflammation, hypertension, thrombus, cerebral apoplexy, or asthma in mammals, diseases mediated by thromboxane A_2, was enabled based on the disclosure of *in vitro* inhibitory action for thromboxane synthetase and the finding that a skilled worker in the pharmaceutical arts can determine details such as dosages without "inventive skill or undue experimentation". *Id.* at 1051.

The Patent Office cites several references in the context of *In re Wands*[3] as evidence for its conclusion that the overall effect of STAT6 inhibition is hard to predict[4] and therefore the subject matter of the claims is not enabled. Applicants address each of the *Wands* factors in turn and show that the references that the Patent Office cites either do not accurately address the *in vitro* assays used in the present invention and/or misinterpret the author's own conclusions as to the correlation of STAT6 inhibition with the ability to treat asthma *in vivo*.

i. Breadth of the Claims.

Claims 33-64 relate to compositions comprising the enabled and useful compounds of the invention. With regard to the method claims, the Patent Office alleges that asthma is not representative of the various other conditions cited in method claim 97.

Without acquiescing to the Patent Office's position and in order to expedite prosecution of the present application, Applicants note that they have amended base claim 65 to remove the recital of conditions other than asthma.

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[3] As noted by the Examiner, whether undue experimentation is required to practice an invention is typically determined by evaluating: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation'" in determining whether pending claims are enabled. *In re Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

[4] Usually, the issue of *in vitro* and *in vivo* "correlation" is related to the issue of the presence or absence of working examples, not predictability. MPEP 2164.02; U.S. Patent Office's Training Materials for Examining Patent Applications with respect to 35 U.S.C. 112, first paragraph-enablement for chemical and biotechnical applications. As used therein "correlation" refers to the relationship between *in vitro* model assays and a disclosed or a claimed method of use. An *in vitro* example in the specification constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

Claim 65, for instance, has been amended to recite:

> A method for treating asthma in a host in need thereof, comprising administering to said host a therapeutically effective amount of a compound . . ..

Support for this amendment appears on, for example, page 17, second paragraph, and the language of claim 98, which has been canceled. Applicants submit that this renders the Patent Office's arguments as to the inclusion of non-asthmatic conditions as moot. Applicants also submit that this amendment also renders the Patent Office's argument as to use of the term "modulating" moot and places the claims in condition for allowance.

ii. Nature of the Invention.

The invention is pharmaceutical in nature. It is in a field in which the courts have held that the necessary showing for enablement does not require a showing of efficacy in humans[5].

iii and iv. Amount of Guidance Presented and the Presence of Working Examples.

Applicants have identified compounds that inhibit the binding of STAT6 to IL-4R. The compounds of the present invention were identified using a chemiluminescence assay similar to the assay exemplified in U.S. Patent No. 6,207,391 at col. 22, lines 33-61 (this patent issued from U.S. Patent Application No. 09/053,003) and U.S. Patent Nos. 5,618,693; 5,639,858, and 5,756,700 (all incorporated by reference at p. 51, last paragraph in the specification).[6] A detailed description of the assay, including representative receptor peptides, representative

[5] *See* Scott v. Finney, 34 F.3d 1058, 1063, (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

[6] As recited in the MPEP §2164.01 "A patent need not teach, and preferably omits, what is well known in the art."

STAT6 polypeptides and concentration thereof, is provided in U.S. Patent No. 6,207,391 at col. 8, line 13 to col. 18, line 18. The assay methods involve determining whether a test compound decreases or increases the degree of binding of a STAT6 polypeptide to an IL-4R peptide that includes a phosphotyrosine residue. Relative inhibitory concentration of exemplary compounds of the invention at 50% binding of the STAT6 polypeptide to a receptor peptide are disclosed at p. 42-48 of the specification (examples 6, 7 and 8) using the *in vitro* STAT binding assays described above. Thus, Applicants have demonstrated that the compounds of the invention and compositions of the invention inhibit STAT6 function.

Applicants have also demonstrated a nexus between STAT6 function and various conditions, including asthma. The Examiner's attention is respectfully directed to page 4 of the specification, the 6th full paragraph wherein it states:

> The compounds of the present invention are useful in compositions that further comprise a pharmaceutically acceptable excipient. Both the compounds and compositions of the present inventions are useful for the diagnosis and treatment (including prophylactic treatment) of conditions mediated through STAT signaling. Examples of conditions associated with STAT signaling include, but are not limited to: T_H1-mediated conditions such as delayed-type hypersensitivity, contact dermatitis, uveitis, Crohn's disease, psoriasis and autoimmune disease (typically associated with STAT4 signaling); T_H2-mediated diseases such as allergic rhinitis, asthma, scleroderma, eczema and conjunctivitis (typically associated with STAT6 signaling); proliferative disorders such as cancers (associated with STAT3 and/or STAT5 signaling); and STAT1 conditions which are similar to those described for STAT4, but typically observed in more acute situations such as acute transplant rejections. A variety of additional conditions associated with STAT signaling include atopic dermatitis, anaphylaxis, food or drug induced allergy, hypersensitivity reactions, alveolitis, Churg-Strauss syndrome, urticaria, angiodema, and systemic lupus erythematosus.

In addition, methods of formulation and administration of the compounds are disclosed at p. 20-23 of the present specification. Thus, the specification teaches those of skill in the art various conditions and indications wherein the compounds of the present invention are useful and efficacious. These indications include, but are not limited to, asthma. In view of this teaching, a skilled person would be appraised of how to use the present compounds in treating a variety of indications and diseases, including asthma.

While the Patent Office states that it is unknown to which domain within the intact STAT6 protein the claimed peptides might bind and whether tyrosine phosphorylation (on STAT 6 will be inhibited) (Office action at p.5), the specification clearly teaches on page 11, first paragraph, the theorized mode of action of the compounds wherein it states:

> The present invention provides compounds, compositions and methods for the inhibition or treatment of conditions or disorders modulated by the STAT transcription factors, particularly STAT4 and STAT6. Additionally, the compounds are useful for the diagnosis of conditions dependent on STAT signaling. Without intending to be bound by a theory, it is believed that certain compounds of the present invention block interaction between phosphorylated tyrosine residues in the IL-4 receptor and the SH2 domain of STAT6. In this manner, phosphorylation (*i.e.*, activation) of STAT6 by IL-4-receptor-associated kinases is prevented. It is also believed that the compounds exert their effect by interfering with the dimerization of STAT6 monomers that is required before the STAT6 dimer can bind to the STAT6-dependent genes and initiate transcription of, for example, germline epsilon transcript. In view of this transcriptional control, the compounds, compositions and methods of the present invention will be useful in treating (suppressing or inhibiting) the full spectrum of immune disorders which require transcriptional activation-by STAT6 dimer, including allergic conditions (*e.g.*, allergic rhinitis, asthma, atopic dermatitis, contact dermatitis, anaphylaxis, food or drug induced allergy, conjunctivitis, uveitis, hypersensitivity reactions, alveolitis and psoriasis), Churg-Strauss syndrome, delayed-type hypersensitivity, urticaria, angiodema, eczema, scleroderma, and systemic lupus erythematosus.

Thus, it is theorized that certain compounds of the present invention block the interaction between phosphorylated tyrosine residues of the IL-4 receptor and the SH2 domain of STAT6. In this manner, phosphorylation (*i.e.*, activation) of STAT6 by IL-4-receptor-associated kinases is prevented. Moreover, it is believed the compounds and methods of the present invention are useful in treating (suppressing or inhibiting) the full spectrum of immune disorders which require transcriptional activation-by the STAT6 dimer.

Furthermore, it is known, for example, that STAT6 is activated upon binding of the cytokine IL-4 to a cell surface receptor. Activation of STAT6 results in the formation of a STAT dimer, which enters the nucleus of the cell and binds to the regulatory region of a gene inducible by IL-4, thereby triggering transcription of the gene (*see*, U.S. Patent Nos. 6,207,391 and 5,591,825).

In view of the specification's teaching regarding various indications and diseases, it is apparent that a skilled person would be appraised of how to use the invention. Therefore, Applicants respectfully request that the Examiner withdraw the rejection.

v. State of the Art.

The state of the art is high and advanced in this particular field. *In vitro* and *in vivo* methods for determining the effect of modulating the STAT6 pathways effect on asthma *in vitro* and *in vivo* are well known in the art as evidenced in the art cited by the Examiner. Wang *et al.*, for instance, discloses a number of such assays.

vi. Predictability of the Art.

The Patent Office mainly attempts to question whether the *in vitro* assay used is reasonably predictive of *in vivo* activity and attempts to use Wurster *et al.* ("Wurster et al.") *Oncogene* 19(21): 2577-84 (2000); Tomkinson *et al.*("Tomkinson et al.") *Am. J. Resp. and Crit. Care Med. 160*(4): 1283-91 (1999); Foster *et al.* ("Foster et al. ") *Clinical and Exp. Allergy 29*(1) 12-16 (1999) 448; Trifilieff *et al.* ("Trifilieff et al.") *Brit. J. Pharm. 130*(7): 1581-8 (2000);

Henderson *et al.* ("Henderson et al.") *J. Immunol. 164*: 1086-95 (2000); Durbin *et al.* ("Durbin et al.") *Cell 84*(3): 443-50 (1996); Wang et al. ("Wang et al.") *Blood 95*:4 1249-57 (2000); and Mikita *et al.* ("Mikita et al.") *J. Biol. Chem. 273*: 17634 (1998) as evidence in support of its conclusion. Specifically on page 8 of Office Action, the Patent Office questions a) whether small peptides can mimick interactions of large, multifaceted and multifunctional proteins *in vivo*; b) whether the degree of inhibition between STAT6 and IL-4R *in vivo* is sufficient to effectively treat asthma; c) what functions of STAT6 may be inhibited by the compounds and compositions of the invention and what are the effects of such inhibition; and d) whether the compounds of the invention will be effective against all allergens, by any route of administration, at any timing of administration. Applicants address these four subject areas in turn.

a) Whether small molecules can mimick interactions of large, multifaceted and multifunctional proteins to have sufficient activity in vivo and b) whether the degree of inhibition between STAT6 and IL-4R in vivo is sufficient to effectively treat asthma.

The initial burden is on the examiner to give reasons for the lack of enablement, and when possible it should be supported by evidence. Here, the Patent Office offers no evidence in support of its proposition. The Applicants are therefore not required to provide evidence indicative of the claimed compounds ability to mimic larger peptides or treat the indicated disorders *in vivo*. However, in order to expedite prosecution of the present application, Applicants note that Perez-G *et al.* found that aspirin, which is known to improve allergic disease, especially asthma, is an inhibitor of the activation of STAT6 by IL-4 and IL-13 (*see* Perez-G. et al. *J. Immunol.* 168: 1428-34 (2002), enclosed). Aspirin is even smaller than the exemplified compounds of the present invention. Aspirin's proposed mechanism of action is similar to that proposed by the Applicants with regard to their compounds, compositions, and methods (inhibition of STAT6 activation by IL-4R). Applicants contend that this is sufficient evidence to show that there is a reasonable correlation between STAT6 inhibition with small molecules *in vitro* with the ability to treat asthma *in vivo*. Therefore, Applicants respectfully request that the Examiner withdraw the rejection.

c) What functions of STAT6 may be inhibited and what are the in vivo effects of such inhibition especially with regard to d) whether the compounds will be effective against all allergens, by any route of administration, at any timing of administration.

The Patent Office attempts to use the teachings of several references to question how a STAT6 inhibitor might work in treating asthma. As noted above, Applicants respectfully assert that such a showing is not required to enable the claimed invention. In addition, the Patent Office appears to misinterpret the conclusions of these references which generally do not address or question a) the usefulness of any compound or composition of the present invention as an agent to treat asthma, b) the reliability or predictive value of the *in vitro* STAT6 screening assays used in the present invention as a model for asthma therapy; or c) provide any other evidence to cause one of skill in the art to question the asserted utility of Applicants' compositions and methods.

For example, the Patent Office cites Wurster ("Wurster") for its disclosure of five different STAT6 binding domains and concludes that the site of inhibition is "critical" yet the Patent Office gives no reasons for this conclusion. (Office action at p. 5).

Similarly, the Patent Office misinterprets the results and conclusions of Tomkinson *et al.* and Trifilief *et al.*. While Tomkinson *et al.* show that *sensitized* STAT6-deficient mice can develop airway eosinophilia and airway hyperresponsiveness when *reconstituted* with IL-5, they also show that *unsensitized* STAT6-deficient mice do not (p. 1290). Because STAT6 and IL4 also have an effect on T-cells which produce IL-5, Tomkinson *et al.* note that STAT6 has a *critical role* in the development of IL-5 production and subsequent airway eosinophilia and AHR (p. 1290, emphasis added). In fact, Tomkinson *et al.* conclude that STAT6 is critical for the IgE response and highlights "the importance of targeting the STAT6 pathway in the development of new antiallergic asthma drugs." (p. 1290). Tomkinson *et al.* does not stand for the Patent Office's position that only some asthma suffers would benefit from blocking STAT6 when exposed to particular allergens. Applicant's note that a showing that all asthma would benefit is not required for the claimed invention to be enabled. In any case,

Tomkinson *et al.* does not stand for the proposition that persons of skill in the art questioned whether inhibiting STAT6 is reliably predictive of *in vivo* efficacy against asthma.

Likewise, (and as the Patent Office notes) Trifilief *et al.* disclose that during a chronic challenge with aerosolized ovalbumin or phosphate buffered saline that STAT6-deficient mice may still develope inflammatory cell infiltration, IL-4 and IL-5 release, and increased plasma leakage. However, what the Patent Office does not note in its argument is that Trifilief *et al.* also show that the intensity of this inflammation is 80% less than that observed in wild-type mice. (p. 1587). Trifilief *et al.* go on to state that these results suggest that STAT6 signaling is **essential** for the development of allergic airway inflammation following an acute allergen exposure and that it is **partially mediated** by STAT6 in a more chronic situation. (p. 1587). Trifilief *et al.* suggest that **any** asthma sufferer would benefit by blocking STAT6 function which is apposite to what the Patent Office alleges.

The Patent Office cites Durbin *et al.* but this reference relates to STAT1 and does not even mention STAT6. Any suggestion as to STAT6 function is pure conjecture on the part of the Patent Office and does not reflect the teaching of the reference.

The Patent Office attempts to use Foster *et al.* and Henderson *et al.* to support its argument that modulating STAT6 alone may not be effective to treat asthma at any time or by any route of administration. However, the problem with using these references to support such a conclusion is three-fold: 1) A showing that the compounds are effective at all times of administration and by any route of administration is not required for the claimed invention to be enabled, 2) the activity of different class of compounds which act at a different target site is not dispositive on the activity of the compounds, compositions, and methods of the present invention; and 3) in any case, both Foster *et al.* and Henderson *et al.* relate only to STAT-6 activation by IL-4 and not by other cytokines.

Mattes *et al.* (*J. Immunol.* 167: 1683-1692 (2001), enclosed) have shown that IL-13 also plays a key role in the receptor signaling system that involves STAT6 by regulating AHR, mucus hypersecretion, eotaxin production, and eosinophilia in the allergic lung

independently of the IL-4R chain. Mattes *et al.* have also shown that IL-13 did not induce asthma in STAT6-deficient mice.

Therefore when Henderson *et al.* disclose that intranasal but not i.p. administration of a *soluable IL-4 receptor* inhibited an inflammatory response the Patent Office is ignoring any possible effect that IL-13 plays. Likewise, when the Patent Office cites Foster *et al.* for their disclosure of a study by Corry *et al. J. Exp. Med.* 183: 109-17 (1996) disclosing that *anti-IL4 monoclonal antibodies* were effective in abrogating airway hyperreactivity when administered during a period of systemic immunization but not during a period of aerosol challenge, the Patent Office also ignores any possible effect that IL-13 may play. Further, the compositions and methods of the present invention do not comprise soluable IL-4 receptors or anti-IL-4 monoclonal antibodies or act by solely blocking IL-4, therefore the Patent Office's conclusions that the compounds, compositions and methods of the present invention are not not enabled are unfounded.

Finally, the Patent Office also cites Wang *et al.* and Mikita *et al.* for the proposition that it is possible to inhibit one of the functions of STAT6 without inhibiting other functions. While this may be true, Mikita *et al.* and Wang *et al.* make no conclusion that inhibiting STAT6, especially the SH2 binding domain, does not reasonably correlate with the treatment of asthma.

vii. Quantity of Experimentation Necessary.

The field of the invention is the pharmaceutical arts. A great deal of experimentation is quite routine in this field. It is a field which is largely devoted to the screening and testing of a large number of candidate compounds, compositions and treatments in model systems. Indeed, The Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988).

The specification sets forth a method for determining dose/response at page 22, lines 17-27:

> In therapeutic use as immunomodulators, the compounds utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.05 mg/kg to about 20 mg/kg daily. A daily dose range of about 0.05 mg/kg to about 0.2 mg/kg being most preferred. The dosages, however may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increase by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

In fact very little additional experimentation would be required to practice other embodiments of the invention. The subject matter of the anti-asthma therapy is well exemplified in the specification. The relative activity of the compounds used in the compositions and methods of the invention are well-exemplified in Examples 6-8.

viii. Relative Skill of those in the Art.

The Patent Office does not specifically address this factor but Applicants submit that the relative skill of those in the art is high.

Overall Summary of the Wands Analysis

Here,

(i) the relative skill and experience of those in the art of asthma therapeutics is generally quite high;

(ii) the nature of the invention involves testing compounds in model test systems which are well recognized in the art as important models for the modulation of asthma;

(iii) the breadth of the claims is commensurate with the specification disclosure;

(iv) the specification provides adequate guidance for all manipulations required to practice the invention;

(v) the specification provides working examples of the claimed subject matter;

(vi) the state of the art is high, involving administering pharmaceutical agents;

(vii) noting that FDA standards as to operability are not those set forth for patentability, the art is sufficiently predictable such that one of ordinary skill in the art would consider the disclosed data to support the operability of the claimed subject matter;

(viii) while the field of art is one in which a great deal of experimentation is routinely performed by a person of ordinary skill in the art, in fact relatively little additional research would be required to practice the invention.

In view of the above, Applicants believe that one of ordinary skill in the art could practice the invention using an amount of experimentation which would be routine in the art. Applicants therefore request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 33-64 under 35 U.S.C. § 112, first paragraph, for use of the term "pharmaceutical."

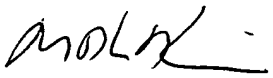
Further, the Examiner rejected claims 33-64 under 35 U.S.C. § 112, first paragraph, for use of the term "pharmaceutical." While Applicants disagree with the Patent Office's assessment of the use of this term, Applicants have deleted the term "pharmaceutical" in claims 33-64 with the understanding this amendment does not limit the original scope of the claim. In view of the amendment to claims 33-64, Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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